Available online at www.sciencedirect.com
SciVerse ScienceDirect
Neuromuscular Disorders 22 (2012) 534–540
www.elsevier.com/locate/nmd

Rippling muscle disease and facioscapulohumeral dystrophy-like phenotype in a patient carrying a heterozygous *CAV3* T78M mutation and a D4Z4 partial deletion: Further evidence for "double trouble" overlapping syndromes

Giulia Ricci [a,*], Isabella Scionti [c], Greta Alì [b], Leda Volpi [a], Virna Zampa [d], Marina Fanin [e], Corrado Angelini [e], Luisa Politano [f], Rossella Tupler [c], Gabriele Siciliano [a]

[a] *Department of Neuroscience, University of Pisa, Pisa, Italy*
[b] *Department of Surgery, University of Pisa, Pisa, Italy*
[c] *Department of Biomedical Sciences, University of Modena and Reggio Emilia, Modena, Italy*
[d] *Department of Radiology, University of Pisa, Pisa, Italy*
[e] *Department of Neurosciences, University of Padua, Padua, Italy*
[f] *Department of Experimental Medicine, Cardiomyology and Medical Genetics 2nd University of Naples, Naples, Italy*

Received 8 August 2011; received in revised form 11 November 2011; accepted 1 December 2011

Abstract

We report the first case of a heterozygous T78M mutation in the caveolin-3 gene (*CAV3*) associated with rippling muscle disease and proximal myopathy. The patient displayed also bilateral winged scapula with limited abduction of upper arms and marked asymmetric atrophy of leg muscles shown by magnetic resonance imaging. Immunohistochemistry on the patient's muscle biopsy demonstrated a reduction of caveolin-3 staining, compatible with the diagnosis of caveolinopathy. Interestingly, consistent with the possible diagnosis of FSHD, the patient carried a 35 kb D4Z4 allele on chromosome 4q35. We discuss the hypothesis that the two genetic mutations may exert a synergistic effect in determining the phenotype observed in this patient.

Keywords: Rippling muscle disease; Caveolinopathy; Facioscapulohumeral dystrophy; Limb girdle muscular dystrophy type 1C

1. Introduction

Caveolinopathies, clinically heterogeneous neuromuscular and/or cardiac diseases, mainly present as limb girdle muscular dystrophy type 1C (LGMD-1C) or inherited rippling muscle disease (RMD), characterized by electrically silent percussion-induced muscle mounding. However, these disorders also include isolated hyperCKemia, distal myopathy (MD) [1,2], familial hypertrophic cardiomyopathy (HCM) [3], arrhythmogenic long QT syndrome (LQTS) [4] and some cases of sudden infant death syndrome (SIDS) [5]. All these disorders are usually transmitted as an autosomal dominant trait and are caused by mutations in the *CAV3* gene (OMIM 601253, gene map locus 3p25), which encodes for caveolin-3 (Cav-3), the myocyte-specific isoform of caveolin proteins. Caveolins are the main protein components of caveolae, vesicular invaginations of the plasma membrane involved in several biological processes such as cellular vesicular trafficking, endocytosis, cholesterol homeostasis, and signal transduction [6,7]. Functional studies of different *CAV3* missense mutations have shown that mutant Cav-3 can be held in the Golgi apparatus and rapidly degraded by the ubiquitin–proteasome system, exerting a dominant negative effect on the wild-type protein [8–10], thereby explaining the dominance of these

* Corresponding author.
E-mail address: g_ricci@alice.it (G. Ricci).

0960-8966
doi:10.1016/j.nmd.2011.12.001

mutations. The same mutation can be associated with different phenotypes, sometime overlapping, in different individuals, suggesting that additional unknown loci affect the disease phenotypes. However, muscle impairment and cardiac dysfunction rarely coexist in a patient, probably due to the involvement of distinct pathogenic molecular pathways [11,12].

Facioscapulohumeral muscular dystrophy (FSHD) is an autosomal dominant neuromuscular disorder, characterized by progressive weakness of the facial, shoulder girdle and upper limb muscles, often involving peroneal and pelvic girdle muscles. The molecular bases of this disease are unknown, but the disorder is associated with DNA rearrangements of a polymorphic array of tandemly repeated 3.3 kb DNA segments (named D4Z4 repeats) located at the subtelomeric region of chromosome 4q [13]. It has been established that normal subjects carry p13E-11 EcoRI digested alleles larger than 50 kb ($\geqslant$11 D4Z4 repeats) originating from chromosome 4, while the majority of either *de novo* or familial FSHD patients carries alleles of 35 kb, corresponding to 8 D4Z4 units, or shorter [14]. Genotype–phenotype correlation studies have revealed an inverse correlation between the number of D4Z4 repeats and the severity of the disease. Nevertheless, the variability of clinical outcomes has resulted to be more pronounced than expected [15,16], even within the same family [17,18]. In addition, subjects carrying reduced D4Z4 allele without signs of the disease have also described [15,16,19]. To explain the clinical variability and the presence of non-penetrant carriers, recent studies have suggested that reduction of D4Z4 repeats on chromosome 4q35 is pathogenic only in certain "permissive" chromosomal backgrounds, such as polymorphisms that map at the distal region of chromosome 4q and chromosome 10q [20–22].

Here we report on a patient with rippling myopathy, limb girdle muscle weakness and some phenotypic features reminiscent of FSHD, who proved to be a carrier of a heterozygous *CAV3* mutation and a D4Z4 FSHD-sized allele. *The observed phenotype was consistent with these combined genetic mutations in determining an "overlapping" syndrome.*

2. Case description

The proband, a 55-year-old Caucasian male, born to non-consanguineous parents, was delivered at term after an uneventful pregnancy. He achieved normal developmental motor milestones. His remote pathological anamnesis was unremarkable. At the age of 45, the patient began to complain of limb girdle fatigability and muscle weakness with difficulty in some motor tasks, such as raising the upper limbs or climbing stairs. Since the age of 53, he had also been experiencing muscle cramps, pain, stiffness induced by exercise and the occurrence of localized mounding and rapid contractions of lower limb muscles, generally caused by muscle percussion. Neurological examination revealed a hyperlordotic posture, bilateral mild winged scapula (Fig. 1), a partial limitation of arms abduction, up to 90°, and a moderate hyposthenia at the pelvic girdle muscle level (score 4.5 at MRC grading Hammersmith Hospital motor scale [23]). Mechanical percussion of thigh muscle bellies induced a transient local mounding phenomenon, resembling RMD [24]. The deep tendon reflexes were mildly reduced. No signs of facial weakness were present. The family history was inconsistent, although his father was reported to have difficulties in raising arms in his seventies and his mother, who died at age of 70 years from congestive heart failure, was reported to have heart complaints since age of 35 years, after her last delivery (medical reports are not available) (Fig. 2).

Blood creatine kinase (CK) level was mildly increased (up to 1000 U/L; n.v. <190); the routine blood tests and thyroid hormones were in the normal range. The ischemic forearm exercise test for lactate dosage showed a delayed recovery in lactate kinetics after-exercise. Needle electromyography revealed myopathic signs in the four limbs; the involuntary rolling muscle contractions were electrically silent. In order to exclude an immunogenic form of

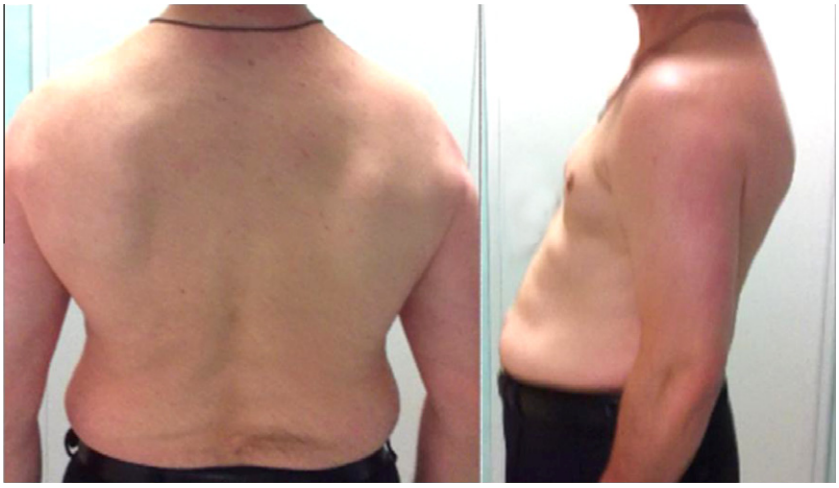

Fig. 1. Proband with bilateral mild winged scapula and hyperlordotic posture.

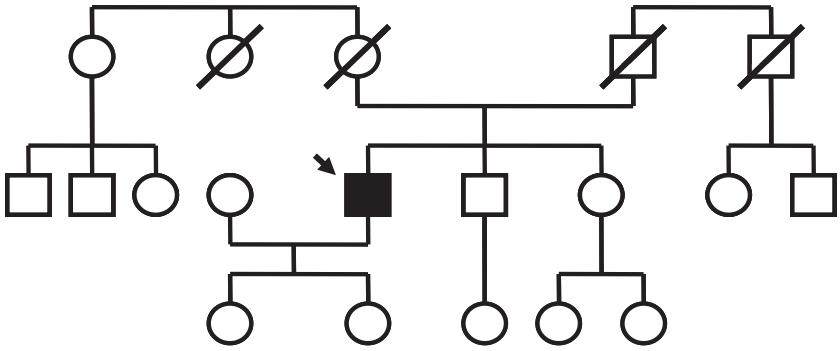

Fig. 2. Pedigree of the proband family. Arrow indicates the proband. Proband's father was reported to have difficulties in raising arms in his seventies; he died at the age of 83 years for Parkinson's disease. Proband's mother, affected by congestive heart failure, died at the age of 70 years (medical reports are not available). The brother, the sister and the two daughters of the proband resulted completely asymptomatic.

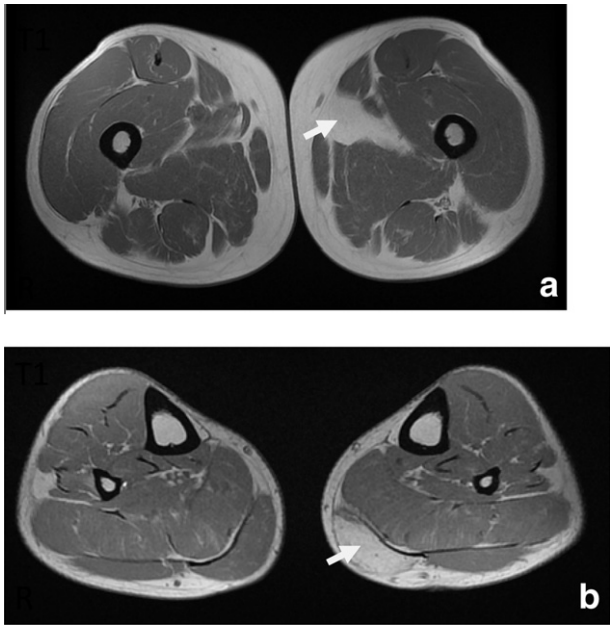

Fig. 3. T1-weighted skeletal muscle MRI of the lower limbs: (a) at thigh level, marked fatty infiltration and atrophy of the left long adductor (arrow); (b) at leg level, fatty infiltration of the medial head of the left gastrocnemius (arrow).

RMD, such as associated with myasthenia gravis [25,26], levels of anti-acetylcholine receptor-antibodies were determined with a negative result; thoracic computed tomography was inconsistent. Cardiac assessment was normal.

Thigh and leg muscle magnetic resonance imaging (MRI) revealed an asymmetric muscle pattern involvement, with marked fatty infiltration and atrophy of long adductor of the left thigh and medial head of the left gastrocnemius (Fig. 3), mild signs of edema in thigh muscles (right femoral biceps and left gracile muscles) and in leg muscles (lateral head of the right gastrocnemius and bilateral tibial anterior).

The patient underwent biopsy at the right quadriceps *femoris* muscle. The frozen muscle specimen was processed for routine histology and immunohistochemistry analysis. Muscle biopsy showed moderate myopathic changes including increase in connective tissue and diameter variability in both fiber types, scattered round shaped atrophic fibers, rare degenerative fibers and a considerable endomysial inflammatory infiltrate (Fig. 4). Immunostaining, performed for dystrophin (dilution 1:20), laminin (dilution 1:50), alfa-sarcoglycan (dilution 1:100), dysferlin (dilution 1:20) and emerin (dilution 1:20) (mouse monoclonal antibodies; Novocastra Ltd., United Kingdom) using a Benchmark immunostainer (Ventana Medical System, Tucson, AZ), was normal.

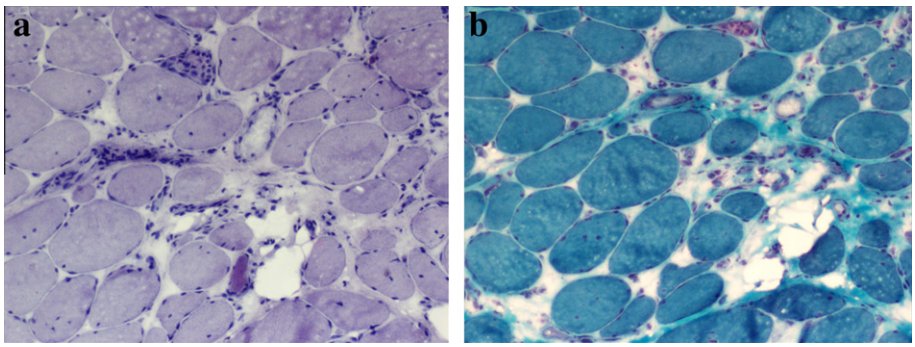

Fig. 4. Quadriceps *femoris* muscle biopsy: (a) hematoxylin and eosin and (b) modified Gomori's trichrome staining; magnification 20×. Increase in connective tissue and diameter variability in both fiber types, scattered round shaped atrophic fibers, rare degenerative fibers and a considerable endomysial inflammatory infiltrate.

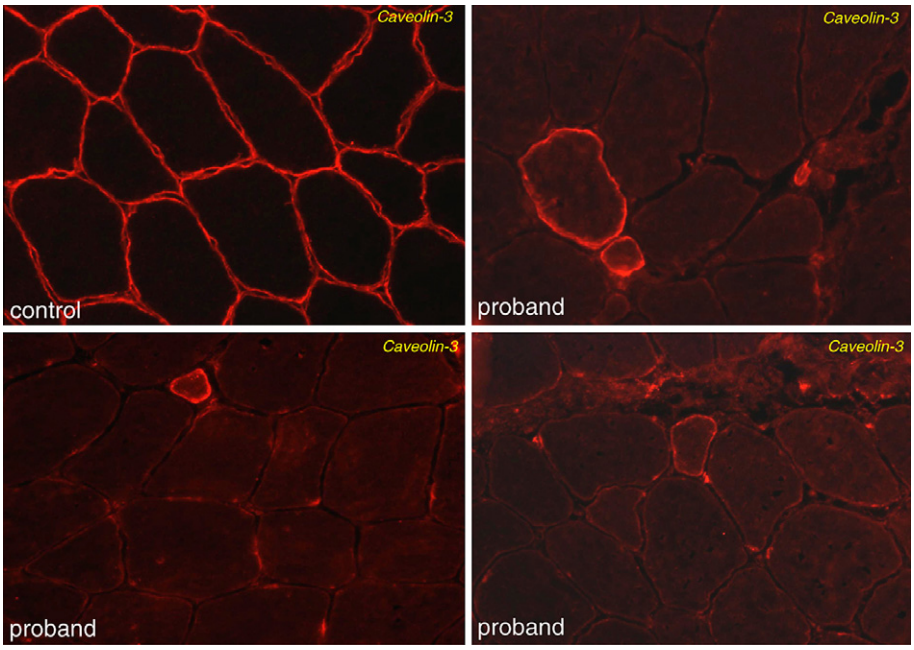

Fig. 5. Skeletal muscle immunostaining for Cav-3 (monoclonal antibodies diluted 1:100 in 1% BSA-PBS; Transduction Laboratories, Lexington, KY) of a healthy control and of the proband. In the proband the immunolabeling for Cav-3 resulted markedly reduced at the plasmalemma in almost all fibers.

Genetic analysis for *CAV-3* gene was performed. High molecular weight genomic DNA was extracted from peripheral blood lymphocytes with standard procedures. Using polymerase chain reaction (PCR), denaturing high-performance liquid chromatography, and direct DNA sequencing, the open reading frame/splice site mutational analysis on *CAV3* revealed n.233C > T (T78M) missense mutation in exon 2, involving a highly conserved residue in the Cav-3 transmembrane domain [10]. Subsequently skeletal muscle immunostaining for Cav-3 (monoclonal antibodies diluted 1:100 in 1% BSA-PBS; Transduction Laboratories, Lexington, KY) was carried out and resulted markedly reduced at the sarcolemma in almost all fibers (Fig. 5), compatible with diagnosis of caveolinopathy [1].

Based on some phenotypic features of the patient, such as bilateral mild winged scapula and upper limb girdle weakness as well as muscle MRI pattern, facioscapulohumeral muscular dystrophy (FSHD) was also considered. The molecular test for FSHD, Southern blot hybridization of EcoRI/BlnI-digested DNA resolved by pulsed field gel electrophoresis detected with probe p13-E11 [13], revealed an EcoRI restriction fragment of 35 kb on chromosome 4q35. Polymorphisms flanking the D4Z4 repeat array were also investigated. The 35 kb D4Z4 allele was associated with 4qA variant, 161 Simple Sequence Length Polymorphism (SSLP) and the permissive Single Nucleotide Polymorphism (SNP) ATTAAA [20–22].

Molecular analysis for *CAV3* gene and FSHD in other family members (brother, sister and daughters), all completely asymptomatic, was not performed because they declined to undergo genetic testing.

3. Discussion

We report the first case of a heterozygous *CAV3* T78M mutation associated with rippling muscle disease and proximal weakness in which immunohistochemical analysis of skeletal muscle confirmed reduced Cav-3 immunolabeling. The heterozygous n.233C > T missense mutation in *CAV3* observed in our case is responsible of a threonine to methionine substitution at codon 78 (T78M), a highly conserved residue of Cav-3. This mutation has originally been reported in three unrelated individuals with long QT syndrome (LQTS) [4]. In particular, one patient, a 14-year-old girl with non-exertional syncope and a 'seizure-like' presentation, carried biallelic digenic mutations, a A913V mutation in the LQT2-associated KCNH2 gene as well as the T78M mutation. In contrast, the other two patients with T78M mutations, an 8-year-old boy with non-exertional syncope and marked sinus bradycardia, and an asymptomatic 40-year-old male, resulted negative for mutations in known LQTS genes. A positive family history was reported in all three patients, but molecular analysis in other family members was not performed. Subsequently, Cronk et al. (2007) [5] has identified the same mutation in heterozygosis in a 2-month-old black female infant who died of SIDS. As this patient presented neither primary cardiomyopathy nor skeletal muscle impairment, it was speculated that Cav-3 might have a role in cardiac excitability. Indeed, Cav-3 co-localizes with beta2-adrenoreceptors in ventricular and sinoatrial myocytes, thus supporting the idea that disruption of caveolae can affect the beta-adrenergic responsiveness and the excitation–contraction coupling of cardiac myocytes [27–29]. The *CAV3*

T78M mutation has also been found in a subject with idiopathic hyperCKemia, although in this case immunohistochemical analysis of Cav-3 in a muscle biopsy was normal [30]. More recently, Traverso and coworkers (2008) [10] have described homozygous T78M mutation in *CAV3* in a 58-year-old woman born to consanguineous parents, affected by dilated cardiomyopathy and limb girdle muscular dystrophy. The patient's daughter, heterozygous for the mutation, was asymptomatic and had normal CK, suggesting an autosomal recessive mode of inheritance for this trait. *In vitro* studies showed that T78M mutated Cav-3 impairs the ability of the Cav-3 hydrophobic domain to assembly Cav-3 homo-oligomers units for the formation of caveolae in muscle cells. Thus it was concluded that the T78M mutation acts through a loss-of-function mechanism [31–33]. This hypothesis was consistent with the fact that the patient carrying a homozygous *CAV3* T78M substitution developed a severe muscular phenotype, whereas her heterozygous daughter was asymptomatic.

Collectively, published data [4,5,10,30] do not fully support the hypothesis that *CAV3* T78M mutation is pathogenic in the skeletal muscle in the heterozygous state. Instead, it can be hypothesized that the *CAV3* T78M mutation may exert a pathogenic effect in association with other genetic factors Indeed, genotype–phenotype correlation studies suggest that in caveolinopathies genetic modifiers may contribute to determine Cav-3 deficiency phenotype [1,10,12,34].

In our case, the clinical diagnosis of caveolinopathy was suggested by the presence of rippling phenomenon and proximal muscle weakness resembling a LGMD phenotype and was supported by the discovery of *CAV3* T78M mutation. The histochemical analysis performed on skeletal muscle biopsy revealed reduced immunolabeling for Cav-3, compatible with diagnosis of caveolinopathy [1]. However, the shoulder girdle involvement presenting with scapular winging observed in our case is unusual in caveolinopathies, although these disorders are associated with a broad spectrum of clinical phenotypes [12,35]. Beyond the bilateral winged scapula and the limitation of upper arms abduction, the patient also displayed other clinical features reminiscent of FSHD, such as marked asymmetry at MRI imaging of muscle involvement in the legs [36,37] and the inflammatory infiltration observed in muscle biopsy [38]. Consistent with these clinical observations we detected a 35 kb D4Z4 allele on chromosome 4q35, which is generally reported in patients with a mild FSHD phenotype [39]. Further, this was also associated with the 161A-SNP ATTAAA permissive haplotype [22], recently proposed as the genetic marker for FSHD [40]. Nevertheless, weakness of the pelvic girdle muscles, as complained by our patient, is not usually present at onset in FSHD [41] and the rippling phenomenon, specific sign of caveolinopathy, has never been reported associated with D4Z4 reduced allele.

The extensive use of the molecular analysis as diagnostic test in human hereditary myopathies has led to the identification of an increasing number of atypical phenotypes. This is particularly true for FSHD, in which various clinical features have been found in subjects carrying FSHD-sized D4Z4 alleles, including a facial-sparing form of FSHD (SHD) [42], limb-girdle muscular dystrophy [43], distal myopathy [44], asymmetric brachial weakness [43], chronic progressive external ophthalmoplegia [45], asymptomatic hyperCKemia [46], hypertrophic cardiomyopathy [47], adult-onset distal myopathies with rimmed vacuoles [48], isolated axial myopathy with camptocormia and bent spine syndrome [49,50]. In addition, overlapping FSHD phenotypes in which 4q35 deleted D4Z4 mutation is associated with other pathogenic mutations in other genes, have been reported in cases of patients with mitochondrial myopathy/FSHD [51], Becker dystrophy/FSHD [52], Duchenne dystrophy/FSHD [53,54], Leber's hereditary optic neuropathy/FSHD [55], suggesting a synergistic effect of those simultaneous mutations in reaching disease threshold and determining overlapping phenotypes.

In conclusion, our case may represent a further example of such atypical phenotypes in which D4Z4 deletion contributes to pathogenicity of heterozygous *CAV3* T78M mutation for the observed myopathic phenotype, resulting in an overlapping syndrome.

Acknowledgment

Grant support was received from Telethon GUP08004 GS (RT), AFM 14339 (RT), NIH-NINDS R01 047584 (RT).

References

[1] Fulizio L, Nascimbeni AC, Fanin M, et al.. Molecular and muscle pathology in a series of caveolinopathy patients. Hum Mutat 2005;25:82–9.
[2] Bruno C, Sotgia F, Gazzerro E, Minetti C, Lisanti MP. Caveolinopathies. In: Pagon RA, Bird TD, Dolan CR, Stephens K, editors. Seattle (WA): University of Washington, Seattle 2007; 1993.
[3] Hayashi T, Arimura T, Ueda K, et al.. Identification and functional analysis of a caveolin-3 mutation associated with familial hypertrophic cardiomyopathy. Biochem Biophys Res Commun 2004;313:178–84.
[4] Vatta M, Ackerman MJ, Ye B, et al.. Mutant caveolin-3 induces persistent late sodium current and is associated with long-QT syndrome. Circulation 2006;114:2104–12.
[5] Cronk LB, Ye B, Kaku T, et al.. Novel mechanism for sudden infant death syndrome: persistent late sodium current secondary to mutations in caveolin-3. Heart Rhythm 2007;4(2):161–6.
[6] Monier S, Parton RG, Vogel F, Behlke J, Henske A, Kurzchalia TV. VIP21-caveolin, a membrane protein constituent of the caveolar coat, oligomerizes in vivo and in vitro. Mol Biol Cell 1995;6:911–27.
[7] Galbiati F, Razani B, Lisanti MP. Caveole and caveolin-3 in muscular dystrophy. Trends Mol Med 2001;7:435–41.
[8] Galbiati F, Volonte D, Minetti C, Chu JB, Lisanti MP. Phenotypic behavior of caveolin-3 mutations that cause autosomal dominant limb girdle muscular dystrophy (LGMD-1C). Retention of LGMD-1C caveolin-3 mutants within the golgi complex. J Biol Chem 1999;274:25632–41.
[9] Galbiati F, Volonte D, Minetti C, Bregman DB, Lisanti MP. Limb-girdle muscular dystrophy (LGMD-1C) mutants of caveolin-3 undergo ubiquitination and proteasomal degradation. Treatment with proteasomal inhibitors blocks the dominant negative effect of

LGMD-1C mutanta and rescues wild-type caveolin-3. J Biol Chem 2000;275:37702–11.
[10] Traverso M, Gazzerro E, Assereto S, et al.. Caveolin-3 T78M and T78K missense mutations lead to different phenotypes in vivo and in vitro. Lab Invest 2008;88(3):275–83.
[11] Catteruccia M, Sanna T, Santorelli FM, et al.. Rippling muscle disease and cardiomyopathy associated with a mutation in the CAV3 gene. Neuromuscul Disord 2009;19(11):779–83.
[12] Gazzerro E, Sotgia F, Bruno C, Lisanti MP, Minetti C. Caveolinopathies: from the biology of caveolin-3 to human diseases. Eur J Hum Genet 2010;18(2):137–45.
[13] Wijmenga C, Hewitt JE, Sandkuijl LA, et al.. Chromosome 4q DNA rearrangements associated with facioscapulohumeral muscular dystrophy. Nat Genet 1992;2(1):26–30.
[14] Sarfarazi M, Wijmenga C, Upadhyaya M, et al.. Regional mapping of facioscapulohumeral muscular dystrophy gene on 4q35: combined analysis of an international consortium. Am J Hum Genet 1992;51(2):396–403.
[15] Ricci E, Galluzzi G, Deidda G, et al.. Progress in the molecular diagnosis of facioscapulohumeral muscular dystrophy and correlation between the number of KpnI repeats at the 4q35 locus and clinical phenotype. Ann Neurol 1999;45(6):751–7.
[16] Tonini MM, Passos-Bueno MR, Cerqueira A, Matioli SR, Pavanello R, Zatz M. Asymptomatic carriers and gender differences in facioscapulohumeral muscular dystrophy (FSHD). Neuromuscul Disord 2004;14(1):33–8.
[17] Tupler R, Barbierato L, Memmi M, et al.. Identical de novo mutation at the D4F104S1 locus in monozygotic male twins affected by facioscapulohumeral muscular dystrophy (FSHD) with different clinical expression. J Med Genet 1998;35(9):778–83.
[18] Fitzsimons RB. Facioscapulohumeral muscular dystrophy. Curr Opin Neurol 1999;12(5):501–11.
[19] van Overveld PG, Lemmers RJ, Deidda G, et al.. Interchromosomal repeat array interactions between chromosomes 4 and 10: a model for subtelomeric plasticity. Hum Mol Genet 2000;9(19):2879–84.
[20] Lemmers RJ, Wohlgemuth M, Frants RR, Padberg GW, Morava E, van der Maarel SM. Contractions of D4Z4 on 4qB subtelomeres do not cause facioscapulohumeral muscular dystrophy. Am J Hum Genet 2004;75(6):1124–30.
[21] Lemmers RJ, Wohlgemuth M, van der Gaag KJ, et al.. Specific sequence variations within the 4q35 region are associated with facioscapulohumeral muscular dystrophy. Am J Hum Genet 2007;81(5):884–94.
[22] Lemmers RJ, van der Vliet PJ, Klooster R, et al.. A unifying genetic model for facioscapulohumeral muscular dystrophy. Science 2010;329(5999):1650–3.
[23] John J. Grading of muscle power: comparison of MRC and analogue scales by 279 physiotherapists. Medical research council. Int J Rehabil Res 1984;7:173–81.
[24] Wiwanitkit V. Bedside diagnosis of rippling muscle disease. Muscle Nerve 2011;43(1):144.
[25] Schoser B, Jacob S, Hilton-Jones D, et al.. Immune-mediated rippling muscle disease with myasthenia gravis: a report of seven patients with long-term follow-up in two. Neuromuscul Disord 2009;19(3):223–8.
[26] Liewluck T. Immune-mediated rippling muscle disease: another inflammatory myopathy in myasthenia gravis. Arch Neurol 2010;67(7):896–7.
[27] Balijepalli RC, Foell JD, Hall DD, Hell JW, Kamp TJ. Localization of cardiac L-type Ca(2+) channels to a caveolar macromolecular signaling complex is required for beta(2)-adrenergic regulation. Proc Natl Acad Sci USA 2006;103:7500–5.
[28] Calaghan S, White E. Caveolae modulate excitation-contraction coupling and beta2-adrenergic signalling in adult rat ventricular myocytes. Cardiovasc Res 2006;69:816–24.
[29] Barbuti A, Terragni B, Brioschi C, DiFrancesco D. Localization of f-channels to caveolae mediates specific beta2-adrenergic receptor modulation of rate in sinoatrial myocytes. J Mol Cell Cardiol 2007;42:71–8.
[30] Reijneveld JC, Ginjaar IB, Frankhuizen WS, Notermans NC. CAV3 gene mutation analysis in patients with idiopathic hyper-CK-emia. Muscle Nerve 2006;34(5):656–8.
[31] Parton RG. Caveolae and caveolins. Curr Opin Cell Biol 1996;8:542–8.
[32] Das K, Lewis RY, Scherer PE, et al.. The membrane-spanning domains of caveolins-1 and -2 mediate the formation of caveolin heterooligomers. Implications for the assembly of caveolae membranes in vivo. J Biol Chem 1999;274:18721–8.
[33] Schlegel A, Lisanti MP. A molecular dissection of caveolin-1 membrane attachment and oligomerization. Two separate regions of the caveolin-1 C-terminal domain mediate membrane binding and oligomer/oligomer interactions in vivo. J Biol Chem 2000;275:21605–17.
[34] Fee DB, So YT, Barraza C, et al.. Phenotypic variability associated with Arg26Gln mutation in caveolin3. Muscle Nerve 2004;30:375–8.
[35] Aboumousa A, Hoogendijk J, Charlton R, et al.. Caveolinopathy – New mutations and additional symptoms. Neuromuscul Disord 2008;18(7):572–8.
[36] Olsen DB, Gideon P, Jeppesen TD, Vissing J. Leg muscle involvement in facioscapulohumeral muscular dystrophy assessed by MRI. J Neurol 2006;253(11):1437–41.
[37] Kan HE, Scheenen TW, Wohlgemuth M, et al.. Quantitative MR imaging of individual muscle involvement in facioscapulohumeral muscular dystrophy. Neuromuscul Disord 2009;19(5):357–62.
[38] Padberg GW. Facioscapulohumeral disease. In: Thesis, University of Leiden, Leiden; 1982:133–134 (p. 23–24).
[39] Butz M, Koch MC, Müller-Felber W, Lemmers RJ, van der Maarel SM, Schreiber H. Facioscapulohumeral muscular dystrophy. Phenotype-genotype correlation in patients with borderline D4Z4 repeat numbers. J Neurol 2003;250(8):932–7.
[40] Tawil R, van der Maarel S, Padberg GW, van Engelen BG. 171st ENMC international workshop: standards of care and management of facioscapulohumeral muscular dystrophy. Neuromuscul Disord 2010;20(7):471–5.
[41] Padberg GW, Lunt PW, Koch M, Fardeau M. Diagnostic criteria for facioscapulohumeral muscular dystrophy. Neuromuscul Disord 1991;1(4):231–4.
[42] Felice KJ, North WA, Moore SA, Matthews KD. FSH dystrophy 4q35 deletion in patients presenting with facial-sparing scapular myopathy. Neurology 2000;54:1927–31.
[43] Felice KJ, Moore SA. Unusual clinical presentations in patients harboring the facioscapulohumeral dystrophy 4q35 deletion. Muscle Nerve 2000;24:352–6.
[44] van der Kooi AJ, Visser MC, Rosenberg N, et al.. Extension of the clinical range of facioscapulohumeral dystrophy: report of six cases. J Neurol Neurosurg Psychiatry 2000;69(1):114–6.
[45] Krasnianski M, Eger K, Neudecker S, Jakubiczka S, Zierz S. Atypical phenotypes in patients with facioscapulohumeral muscular dystrophy 4q35 deletion. Arch Neurol 2003;60(10):1421–5.
[46] Zouvelou V, Manta P, Kalfakis N, Evdokimidis I, Vassilopoulos D. Asymptomatic elevation of serum creatine kinase leading to the diagnosis of 4q35 facioscapulohumeral muscular dystrophy. J Clin Neurosci 2009;16(9):1218–9.
[47] Tsuji M, Kinoshita M, Imai Y, Kawamoto M, Kohara N. Facioscapulohumeral muscular dystrophy presenting with hypertrophic cardiomyopathy: a case study. Neuromuscul Disord 2009;19(2):140–2.
[48] Reilich P, Schramm N, Schoser B, et al.. Facioscapulohumeral muscular dystrophy presenting with unusual phenotypes and atypical morphological features of vacuolar myopathy. J Neurol 2010;257(7):1108–18.
[49] Jordan B, Eger K, Koesling S, Zierz S. Camptocormia phenotype of FSHD: a clinical and MRI study on six patients. J Neurol 2011;258(5):866–73.
[50] Kottlors M, Kress W, Meng G, Glocker FX. Facioscapulohumeral muscular dystrophy presenting with isolated axial myopathy and bent spine syndrome. Muscle Nerve 2010;42(2):273–5.

[51] Filosto M, Tonin P, Scarpelli M, et al.. Novel mitochondrial tRNA Leu(CUN) transition and D4Z4 partial deletion in a patient with a facioscapulohumeral phenotype. Neuromuscul Disord 2008;18(3): 204–9.
[52] Rudnik-Schöneborn S, Weis J, Kress W, Häusler M, Zerres K. Becker's muscular dystrophy aggravating facioscapulohumeral muscular dystrophy–double trouble as an explanation for an atypical phenotype. Neuromuscul Disord 2008;18:881–5.
[53] Lecky BR, MacKenzie JM, Read AP, Wilcox DE. X-linked and FSH dystrophies in one family. Neuromuscul Disord 1991;1:275–8.
[54] Korngut L, Siu VM, Venance SL, et al.. Phenotype of combined Duchenne and facioscapulohumeral muscular dystrophy. Neuromuscul Disord 2008;18(7):579–82.
[55] Chuenkongkaew WL, Suphavilai R, Vaeusorn L, Phasukkijwatana N, Lertrit P, Suktitipat B. Proportion of 11778 mutant mitochondrial DNA and clinical expression in a Thai population with Leber hereditary optic neuropathy. J Neuroophthalmol 2005;25(3):173–5.